Fort Dodge Animal Health
Division of Wyeth

Internal Correspondence

FORT DODGE

To: NOSB Members **Date:** May 9, 2003

From: Deborah T. Chaleff

Subject: TAP Review Comments

Fort Dodge Animal Health Comments
Technical Advisory Panel Report on Moxidectin and Additional Comments

Fort Dodge Animal Health (FDAH) appreciates the opportunity to comment on the Moxidectin TAP Report. Our comments are listed below:

1. FDAH would like to provide comment on the "STATUS" Section, "International" subsection of the Moxidectin TAP Report. There are numerous government organizations that have made specific recommendations to farmers that tend grazed government properties regarding the use of parasiticide compounds. One FDAH comment can be found (Comment 1) in the Table of Contents of the May 13-14 NOSB Meeting. This comment describes the recommendation by the National Trust (United Kingdom) to use moxidectin based on its preferred safety profile in regard to dung fauna toxicity. In addition, avermectins are specifically banned from use on Trust properties.

Two additional organizations, Bioland in Germany and the Natural Heritage Trust of Australia recommend the use of moxidectin. Their positions are briefly outlined herein.

Germany

"Guidelines for the Health of Animals in Ecologically Active Institutions" is a publication of "Bioland – the Association for organic-biological agriculture" in Germany. The 2nd edition was recently published. Part C contains a discussion of parasites in bovines (ruminating cows and calves) and ovines (ewes and lambs). The primary focus for animal health centers on farm management and grazing techniques that establish and maintain uncontaminated pastures. These are described in "Prevention" (Vorbeugung) sections. However, under some circumstances, the use of parasiticides is considered necessary. For example, some weather conditions can cause an inordinate amount of parasite eggs in a pasture. In the "Treatment" (Behandlung) sections, moxidectin is recommended for use under circumstances of very high egg burdens. In addition, due to concern of the development of resistance of sheep stomach and intestinal worms, the use of ivermectin, benzamidazoles, levamisole and morantel should be restricted.

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Indeed, if resistance is anticipated, moxidectin is recommended for use. Moxidectin is also specifically recommended to treat lungworm infection if other measures fail.

Australia

In two publications from the Natural Heritage Trust/AgForce Queensland, entitled "Strategic use of Parasiticides can help your Dung Beetles" and "Consider your Dung Beetles when using Parasiticides", it is stated that moxidectin is safe to use throughout the year with regard to dung beetle safety, whereas the avermectins and synthetic pyrethroids are considered to be high-risk for dung beetles for the six consecutive months during the year when dung beetle activity is greatest. For one species of dung beetle (*Onitis caffer*), this "Danger period" extends to nine months of the year. Moxidectin, when used at the recommended rates for cattle, has no known impact on young and mature adults, breeding females, eggs or larvae for *Onthophagus gazella, O. taurus, Euoniticellus intermedius* and *E. fulvus*. By contrast, all other avermectins, including abamectin, doramectin, eprinomectin and ivermectin cause increased mortality in young adults, eggs and larvae and reduced breeding capability in breeding females. Synthetic pyrethroids such as delatmethrin and cypermethrin cause increased mortality in mature adults as well as the classes affected by the avermectins.

Reviewer #3 commented that "There is no precedent based on the information provided under Status Among U.S. Certifiers and International for the routine use of moxidectin or any other synthetic parasiticide and Canadian regulations permit synthetic parasiticide use only in the "case of disease and health problems" followed by other restrictions". Fort Dodge believes that the German Bioland, the U.K. National Trust, and the Australian Natural Heritage Trust all provide evidence for the recommended use of moxidectin in organically produced animals and in animals grazed on Trust-managed properties.

2. Reviewer #2 raised the question as to whether the organism used in the manufacture of moxidectin is genetically modified or created using other prohibited techniques. Fort Dodge attests that the organism used, *Streptomyces cyaneogriseus* sp. *noncyanogenus* has not been genetically engineered, has never been subjected to any recombinant DNA technology, contains no foreign genes or DNA and hence is not a genetically modified organism. The original isolate was discovered from an Australian soil sample, and produces nemadectin under established, standard fermentation conditions.

3. Fort Dodge does not consider moxidectin to be a synthetic compound. Moxidectin is identical to its precursor, nemadectin (also known as F-alpha), a natural fermentation product of *Streptomyces cyaneogriseus* sp *noncyanogenus*,

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except for the presence of a "methoxime" group instead of a hyrdroxyl group on one of the ring carbons. Therefore, the vast majority of the molecule, on a molecular weight basis, is of natural origin.

4. Although both are macrocyclic lactones, moxidectin is not another ivermectin. It is classified differently, that is, as a member of the milbemycin family of macrocyclic lactones. Although it is structurally similar to ivermectin, the differences in their structures impart important pharmacological and clinical differences:

a) The pharmacokinetics in cattle are different – moxidectin has significantly lower tissue levels in cattle than ivermectin.
b) Unlike the avermectins, residues of moxidectin in treated cattle dung will not affect breeding, egg laying, developing stages or adults of dung beetles
c) Moxidectin is 64 times less toxic to dung beetle larvae than abamectin.
d) Studies have shown that dung from moxidectin-treated cattle degrades at the same rate as that from untreated animals
e) Delayed degradation of dung from ivermectin treated animals has been reported in many scientific studies, and affects the entire soil ecosystem:
    a. Decreased available grazing area
    b. Reduced nitrogen recycling into pasture
    c. Decreased pasture nutrient quality
    d. Decreased soil aeration
    e. Decreased water filtration into soil
    f. Water contamination and algal blooms
f) Moxidectin is permitted for by Bioland organic production systems in Germany; ivermectin is not
g) The National Trust in the United Kingdom does not permit the use of ivermectin in livestock on its properties but does permit moxidectin

5. There is no withholding period (WHP) for milk from dairy cows treated with moxidectin. This zero day WHP was granted to Fort Dodge's Pour-On product by the FDA's Center of Veterinary Medicine. The basis for granting this claim is that there are exceeding low moxidectin residues in milk from treated cattle. More specifically, the residues do not rise above the moxidectin milk tolerance level established by CVM. This tolerance level is based on the analysis of a comprehensive toxicology data package that was submitted in support of the registration of this product by CVM. In addition, a statistical analysis of the residue data was required, and showed that even during "peak residue" period, which is 3 days after treatment, milk from 99% of the treated animals can be expected to contain levels of moxidectin that are well below the government-established tolerance level.

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6. When exposed to the environment, moxidectin binds tightly, indeed essentially irreversibly, to the soil. This is an important facet of the environmental fate of moxidectin, as this tight binding prevents it from entering aquatic systems where moxidectin-sensitive animals reside, such as fish. Moreover, moxidectin is rendered inactive when bound to soil.

Deborah D. Chaleff

Deborah T. Chaleff, Ph.D.

Pooler, Bob

From: Jones, Keith
Sent: Friday, May 09, 2003 2:09 PM
To: Pooler, Bob
Subject: FW: Fort Dodge Animal Health's comments on the Moxidectin TAP Review

FYI - Official comments from Fort Dodge Animal Health.

-----Original Message-----
From: Livestock, NOSB
Sent: Friday, May 09, 2003 1:19 PM
To: Jones, Keith
Subject: FW: Fort Dodge Animal Health's comments on the Moxidectin TAP Review

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From: Deborah Chaleff[SMTP:CHALEFD@PT.FDAH.COM]
Sent: Friday, May 09, 2003 1:16:56 PM
To: Livestock, NOSB
Subject: Fort Dodge Animal Health's comments on the Moxidectin TAP Review
Auto forwarded by a Rule

Please find attached our comments on the above. We greatly appreciate the opportunity to provide our comments, and we hope that they help correct and clarify some issues raised during the course of the review process.

Sincerely,

Deborah T. Chaleff, Ph.D.
Director, Regulatory Affairs
Fort Dodge Animal Health
Princeton, NJ 08543-5366
732-631-5810
chalefd@pt.fdah.com

memo to NOSB - TAP Review comm...

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